Remarks

Claims 7-9, 22-24 and 34-37 are currently under examination and claims 1-6, 10-21, 25-26 and 31-33 have been withdrawn from consideration.

Rejection of claims 7-9, 22-23 and 34-37 under 35 U.S.C. §103

Claims 7-9, 22-23 and 34-37 were rejected under 35 U.S.C. §103 as being unpatentable over Chen, D. F. *et al.* (1997) *Nature* 385: 434 (Ref. C-15 of IDS) in view of Chen, R.-W. *et al.* (1999) *J. Biol. Chem.* 274:6039 (Ref. C-18 of IDS). Applicants respectfully traverse this rejection.

Chen D.F. et al. is relied upon by the Examiner as disclosing "a new strategy for the treatment of injuries to the nervous system establishing that expression of Bcl-2 is required for the promotion of the growth and regeneration of retinal axons." The Examiner states that "Chen D.F. et al. do not expressly disclose using lithium as a factor to stimulate axon growth or the use of peripheral nervous system cells or human cells..."

Chen R.W. et al. is relied upon by the Examiner as disclosing that "lithium ... increases Bcl-2 expression in cerebral granule cells."

It is the Examiner's position that "[a]t the time the invention was made, it would have been *prima facie* obvious to a person of ordinary skill in the art to use lithium as an agent to stimulate axonal growth." The Examiner further states that "[o]ne of ordinary skill in the art would have been motivated to do this because if according to the document of Chen D.F. et al. increase in Bcl-2 expression leads to stimulation of axon growth..., an agent that increases Bcl-2 expression would promote axon regeneration..."

A showing of a *prima facie* case of obviousness requires: (a) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (b) a reasonable expectation of success; and (c) the references teach or suggest all the claim limitations. M.P.E.P. 2143. Applicants respectfully submit that the Examiner failed to establish a *prima facie* case of obviousness at least because there was no reasonable expectation of success that contacting a neural cell with lithium or a salt thereof would stimulate axonal growth. In

particular, at the time the priority application was filed, it was not known what levels of Bcl-2 were necessary to promote axonal growth. Even if Chen R.W. et al. were teaching that lithium induces Bcl-2 expression, there was no evidence that lithium would stimulate Bcl-2 expression to levels and for a time sufficient to promote axonal growth.

Furthermore, treatment of cells with lithium could have resulted in effects in the cell that would have opposed the increase of Bcl-2 and/or the stimulation of axonal growth. As described, e.g., in Chen R.-W. et al., lithium has many biochemical actions, including the "ability to inhibit phosphoinoside turnover and stimulated levels of calcium, influence signal transduction by modulating G-proteins and protein kinase C, and regulate gene expression involving AP-1 DNA binding activity." Chen, R.-W. *et al.* at page 6039. Chen R.-W. et al. describes that lithium also modulates transcription factor DNA binding activity. Chen, R.-W. *et al.* at page 6042.

Thus, it was not until the inventors tested out the effect of lithium on axonal growth, that they found that lithium did promote axonal growth.

Applicants note for the record that, contrary to the Examiner's statement at page 4, the data regarding anti-apoptotic function of Bcl-2 reviewed in Chen D.F. et al. at page 437 does not support the fact that an increase in Bcl-2 expression leads to stimulation of axon growth. In fact, the authors concluded at the same page that "[t]he dissociation between cell survival and axonal growth is supported by our observations."

Thus, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claim 24 under 35 U.S.C. §103

Claim 24 has been rejected under 35 U.S.C. §103 as being unpatentable over Zhang *et al. Proc. Natl. Acad. Sci. U.S.A.* (1996) 93:4504 (Ref. C-12) in view of Chen R.-W. *et al.* (1999) *J. Biol. Chem.* 274:6039 (Ref. C-18 of IDS). Applicants respectfully traverse this rejection.

Zhang et al. is relied upon by the Examiner as disclosing that "overexpression of *bcl-2* cDNA induced extensive neurite outgrowth in Paju tumor cells, which are neural-crest-derived cells (stem cells) that spontaneously undergo differentiation." The Examiner states that "Zhang et al. do not expressly teach using lithium for neurite outgrowth."

Chen R.-W. et al. is relied upon by the Examiner as disclosing that "lithium increases Bcl-2 expression in cultured cerebral granule cells."

It is the Examiner's position that "it would have been *prima facie* obvious to a person of ordinary skill in the art to use lithium as an agent to stimulate axonal growth of a neural cell that is differentiated *in vitro* from a stem cell." The Examiner further stated that "[o]ne of ordinary skill in the art would have been motivated to do this because the document of Zhang et al. clearly establishes the growth promoting function of Bcl-2 specifically with regard to neurite outgrowth in neural cells that are differentiated *in vitro* from stem cells..."

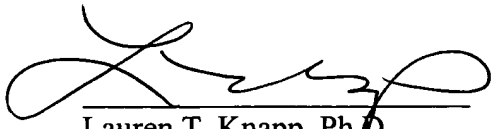
Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness, at least because the Zhang *et al.* and Chen, R.-W. *et al.* do not teach or suggest all the claim limitations. Because these references are limited to neurite growth, they do not teach or suggest that lithium would stimulate the growth of an axon. One having ordinary skill in the art would understand that "neurite" refers to the generic neural cell structures having the potential of forming either axons or dendrites. *See*, for example, *Molecular Biology of The Cell*, 2nd Edition, New York: Garland Publishing, Inc. 1112 (1989); *The Encyclopedia of Molecular Biology*, Oxford: Blackwell Science, Ltd. 709 (1994). Furthermore, neither reference teaches or suggests confirming that the cell grows at least one axon.

Thus, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above remarks, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1000.

Respectfully submitted,
FOLEY HOAG LLP



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